PCT/GB03/02599
10/507293

06 SEP 2004

INVESTOR IN PEOPLE

REC'D 28 APR 2003
WIPO PCT

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears a correction, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

Signed P. Mahoney

Dated 21 March 2003

Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
A
13 MAR 2002
RECEIVED BY FAX

The Patent Office

13MAR02 E703241-1 D02837
P01/7700 0.00-0205898.0

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference P706795GB/DGB

23/3/02
AE WP

2. Patent application number *(The Patent Office will fill in this part)* 0205898.0

13 MAR 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Pharmacia AB
S-112 87
Stockholm
Sweden

UPJOHN COMPANY
301 HENRIETTA STREET
KALAMAZOO
MICHIGAN 49001
UNITED STATES OF AMERICA

Patents ADP number *(if you know it)* 6579570 03

If the applicant is a corporate body, give the country/state of its incorporation: Sweden

DELAWARE

4. Title of the invention: Treatment of Type I diabetes mellitus

5. Name of your agent *(if you have one)*
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

DAVID GARDNER BANNERMAN
WITHERS & ROGERS
Goldings House
2 Hays Lane
London
SE1 2HW

Patents ADP number *(if you know it)* 1776001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

0031367 13 Mar 02 05:32

Patents Form 1/77

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	6 ✓
Claim(s)	1 ✓
Abstract	
Drawing (s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for preliminary examination and search (Patents Form 9/77)	
Request for substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 13 March 2002

12. Name and daytime telephone number of person to contact in the United Kingdom David G Bannerman 01926 336111

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500 505.*
b) *Write your answers in capital letters using black ink or you may type them.*
c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*
d) *If you have answered 'Yes' Patents Form 7/77 will need to be filed.*
e) *Once you have filled in the form you must remember to sign and date it.*
f) *For details of the fee and ways to pay please contact the Patent Office.*

DUPLICATE

P706795GB

Treatment of Type I diabetes mellitus

Diabetes mellitus is a chronic metabolic disorder, which is brought about by either insulin deficiency or insulin resistance. Diabetes mellitus is a disease characterised by physiologic and anatomic abnormalities in many organs, due to vascular abnormalities. However, the most prominent feature of the disease is disturbed glucose metabolism, resulting in hyperglycaemia. Diabetes mellitus is usually divided into two major categories: insulin-dependent diabetes mellitus (Type I diabetes), which usually develops in childhood or adolescence and these patients are prone to ketosis and acidosis. The second category of patients (Type II diabetes) are not insulin dependent and usually manage with diet and oral hypoglycaemic therapy. The annual incidence of Type I diabetes ranges from 10 cases/100000 persons for non-white males to 16 cases/100000 persons for white males in the United States, with equal incidence between males and females. The prevalence of Type I diabetes for all ages in the United States population is 160 cases/100000 persons, with a slightly earlier onset for females with peak age of onset at 10-12 years than for males with peak age of onset at 18 years. Genetic background plays a major role in the development of the disease, with 40% concordance for Type I diabetes exhibited by identical twins and increased incidence among family members. Genes associated with increased susceptibility to Type I diabetes reside near the major histocompatibility complex on chromosome 6, with more than 90% of persons with Type I diabetes featuring DR3 or DR4 haplotypes or both. Likewise, siblings sharing DR3 or DR4 haplotypes from both parents more often than random develop Type I diabetes.

The onset of symptoms in Type I diabetes is usually acute and frequently follows an antecedent viral infection which might be the trigger to a process leading to destruction of the beta cells secondary to auto immune insulitis. When beta cell destruction reaches the critical point, the patient's reduced insulin levels lead to hyperglycaemia with the typical symptomatology of Type I diabetes. At diagnosis approximately 70% of patients with Type I diabetes have antibodies to islet cell cytoplasm i.e. antigens or to components of the islet cell surface. Approximately 15% of patients with Type I diabetes may also show other auto immune features, such as hypothyroidism, Graves' disease, Addison's disease, myasthenia gravis and pernicious anaemia . Autopsies of cases with Type I diabetes show a typical

lymphocytic infiltration in the pancreatic islets .

Treatment of Type I diabetes at present is not satisfactory and the disease leads to serious life-threatening complications that can be only partly overcome with adequate control of insulin levels, which is usually difficult to accomplish in patients with juvenile onset. In addition to the acute diabetic syndrome, chronic manifestations lead to severe arteriosclerosis with microadenopathy affecting the eye with possible early blindness. One in 20 of all Type I diabetes patients becomes blind; about 40% of Type I diabetes develop renal failure, resulting in chronic hemodialisis and/or the need for renal transplantation (4-7). Severe neuropathic changes are also typical for Type I diabetes with many functional disorders associated with sensory, sympathetic and parasympathetic nerves. Cranial nerve, as well as peripheral nerve, may be involved. Treatment of neuropathy remains unsatisfactory, despite normal control of glucose levels with adequate insulin therapy.

Strokes are twice as frequent, myocardial infarctions are 2-5 times as frequent and cardiovascular accidents are 5-10 times more frequent in patients with Type I diabetes than among non-diabetic counterparts. The prognosis of patients with Type I diabetes who survive acute myocardial infarction is 3 times more grave compared to non-diabetics who survive acute infarction and the same is true for other vascular complications. Severe and uncontrollable arteriosclerosis may also be associated with a variety of etiologies involving abnormalities in platelets, clotting factors and lipid carriers, such as HGL levels, as well as uncontrolled diabetes.

The main treatment regime for Type I diabetes involves parental administration of insulin, usually subcutaneously. Insulin is destroyed in the gastrointestinal tract. A common regime for Type I diabetes patients is to inject a combination of short and intermediate acting insulins twice daily, before breakfast and before the evening meal. More intensive routines may involve multiple daily injections or continuous subcutaneous infusion of soluble insulin. The more intensive regimes tend to provide better control of blood glucose; however they are much more intrusive to the patient's life, which can be a particular problem when treating juveniles with this condition. Furthermore the intensive treatment regimes are more expensive.

There are several side effects associated with treatment with insulin, the most important being hypoglycaemia. This is a common side effect, particularly of the more intensive treatment regimes, which can result in severe morbidity and death. The symptoms include muscular weakness, incoordination, confusion and sweating. Severe hypoglycaemia can result in coma. Other side effects include allergy to insulin which may produce local or systemic reactions; loss or proliferation of fat at the sites of injection; and, rebound hyperglycaemia. Rebound hyperglycaemia usually occurs after an unrecognised hypoglycaemic attack, for example during sleep, and is caused by the release of counter-regulatory hormones in response to insulin-induced hypoglycaemia.

In view of the unsatisfactory prognosis for patients with Type I diabetes, and the side effects which may be experienced when using insulin to control the condition, it would be advantageous to have an alternative treatment which could be used instead of, or in combination with insulin. The inventors have considered the use of a growth hormone antagonist as a possible treatment for the condition.

Growth hormone (GH) is secreted by the anterior pituitary gland, under the control of the hypothalamus. It not only regulates growth, but also has metabolic effects, increasing protein synthesis, stimulating lipolysis, and increasing blood glucose. Its effects on carbohydrate metabolism are complex however. The somatogenic effects of GH are primarily mediated by insulin like growth factor-1.

Insulin dependent diabetes causes profound derangement in the GH/IGF-1 axis. In poorly controlled Type 1 diabetics, GH levels are invariably raised. The elevated GH levels are characterised by a greater pulse amplitude and higher baseline concentration of GH as compared to the levels of normal subjects. Recent studies on the signal mode of GH indicate that it is the pulse amplitude rather than the increased baseline which lead to profound changes in insulin resistance in diabetic subjects (Pal et al., Diabetologia, in press). The high GH levels lead to insulin resistance and aggravate the metabolic abnormalities of diabetes. GH excess has also been implicated in the actiology of the dawn phenomenon and may accelerate the development of microangiopathy including

proliferative retinopathy. Finally, an excessive rise in beta hydroxy buturate (BOH) caused by raised GH has been observed, particularly during puberty, and is compounded by the effects of insulin waning overnight; this leads to the risk of rapid decompensation with diabetic ketoacidosis in adolescents with diabetes.

Despite the elevated GH levels, IGF-I levels tend to be low in diabetes and this is related to decreased GH receptor function resulting from low levels of insulin (Holly J.M.P. et al., Clin Endocrinol, 29 (1988) 667-675). The lower IGF-I levels in the presence of elevated GH levels has been implicated in the slow growth and loss of adult height in children with diabetes (Salardi s. et al. Arch Dis. Child, 62 (1987) 57-62).

The mechanism underlying the increased GH levels has been the subject of some controversy. In the diabetic individual hyperglycaemia does not inhibit GH secretion as it does in healthy individuals and it has been proposed that this reflects an altered hypothalamic function. This altered hypothalamic function is characterised by reduced somatostatin levels and resistance to the effects of somatostatin. Suppression of plasma GH by somatostatin analogues and pirenzepine has led to reported improvement in metabolic control. However, this approach has proved inappropriate during childhood and adolescence when growth is rapid as it would inevitably lead to growth failure.

The inventors have surprisingly found that administration of a growth hormone antagonist has a beneficial effect in patients suffering from Type I diabetes mellitus.

The invention provides the use of growth hormone antagonists in the preparation of pharmaceutical compositions for the treatment of Type I diabetes mellitus. The pharmaceutical compositions of the invention may be used to treat mammalian species, in particular, humans, suffering from Type I diabetes mellitus.

Preferably the pharmaceutical composition reduces the patient's insulin requirements, in particular the overnight insulin requirements.

The growth hormone antagonist is preferably Pegvisomant (Somavert).

Further provided by the invention is a method of treating Type I diabetes mellitus comprising the step of administering a growth hormone antagonist to a patient suffering from Type I diabetes mellitus. The patient may be a mammal, particularly a human. Preferably the method of treatment reduces the patient's insulin requirements.

The preferred growth hormone antagonist is Pegvisomant (Somavert). The method of treatment preferably comprises administering between 1mg and 20mg, more preferably between 5mg and 10mg of Pegvisomant (Somavert) once daily.

The invention will now be described in more detail by way of an example.

Methods

7 adolescents of ages ranging from 16-23, the average age being 18, HbA_{1c} 10.0% (7.2-10.8) were randomized in a crossover study comparing Pegvisomant (Somavert) doses 5 mg and 10 mg once daily by subcutaneous injection at 18.00 hours. At baseline and after each 3-week treatment block subjects were admitted for an overnight variable rate insulin infusion (target glucose 5 m/mol/L) and two-step (0.75 and 1.5 ml^{-1}/Kg/min) hyperinsulinaemic euglycaemic clamp.

Results

Data are expressed as mean (SEM).

IGF-1 levels (ngm/L) were reduced from 214.0 (26.4) to 207.1(34.9) after 5 mg Pegvisomant (Somavert) (P=0.7) and 144.2 (26.2) after 10 mg Pegvisomant (Somavert) (P=0.01).

Overnight (03.00-08.00 hours) insulin requirements for euglycaemia (mU/Kg/min) were 0.35(0.03) at baseline, 0.24 (0.04) after 5 mg Pegvisomant (Somavert) (P=0.02) and 0.25 (0.04) after 10 mg Pegvisomant (Somavert) (P=0.01).

Total body glucose disposal (m-value) was not altered during either step of the hyperinsulinaemic clamp (08.00-12.00 hours) by either dose of Pegvisomant (Somavert).

Mean +/- SEM	Baseline	5mg Treatment	10mg Treatment	Combined Treatment
Fasting IGF-I (ng/ml)	214.15 +/- 22.3	207.10 +/- 34.9	144.24 +/- 26.19	175.67 +/- 22.69
Overnight FBG (mmol/l)	5.27 +/- 0.07	5.01 +/- 0.04	5.58 +/- 0.09	5.29 +/- 0.04
Overnight Insulin Requirement (mU/Kg/min)	0.35 +/- 0.04	0.24 +/- 0.01	0.25 +/- 0.02	0.25 +/- 0.01
Overnight Plasma Insulin (mU/l)	16.48 +/- 1.1	19.24 +/- 1.1	14.45 +/- 1.1	16.67 +/- 1.1

Conclusions

Specific GH blockade reduced IGF-I levels and overnight insulin requirements. It did not affect insulin sensitivity the next morning, possibly because of the timing of the clamp or contracting effects of reductions in GH action and IGF-1 on insulin sensitivity. Insulin requirements were reduced by around 31%.

Claims

1. The use of a growth hormone antagonist in the preparation of a pharmaceutical composition for the treatment of Type I diabetes mellitus.
2. The use of a growth hormone antagonist in the preparation of a pharmaceutical composition according to claim 1 for the treatment of mammals.
3. The use of a growth hormone antagonist in the preparation of a pharmaceutical composition according to claim 2 for the treatment of humans.
4. The use of a growth hormone antagonist according to any one of claims 1 to 3 to reduce a patient's insulin requirements.
5. The use of a growth hormone antagonist in the preparation of a pharmaceutical composition according to any one of claims 1 to 4 in which the pharmaceutical composition is Pegvisomant (Somavert).
6. A method of treating Type I diabetes mellitus comprising the step of administering a growth hormone antagonist to a patient suffering from Type I diabetes mellitus.
7. A method of treating Type I diabetes mellitus according to claim 6 in which the patient is a mammal.
8. A method of treating Type I diabetes mellitus according to claim 7 in which the patient is a human.
9. A method of treating Type I diabetes mellitus according to any one of claims 6, 7 or 8 in which the growth hormone antagonist is Pegvisomant (Somavert).
10. A method of treating Type I diabetes mellitus according to any one of claims 6 to 9 in which the method of treatment comprises administering between 1mg and 20mg of Pegvisomant (Somavert) once daily.
11. A method of treating Type I diabetes mellitus according to any one of claims 6 to 10 in which the method of treatment comprises administering between 5mg and 10mg of Pegvisomant (Somavert) once daily.